Should we Still use Nitrous Oxide in our Clinical Practice? No!

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Nitrous oxide – N_2O – had started its career for entertainment purposes (Laughing Gas) in the outgoing 18th century. In 1863 – 15 years after Ether-Day - it was introduced into clinical practice, since then it has been intermittently acted as a party drug ("Eight gr.N_2= equal three Gin tonic") Today it survives in an under-cover-niche as propellant gas in spray-cream containers keeping housewives happy. Though not suitable as sole anaesthetic agent because of its high MAC value of 107-114%, its analgesic properties made it popular among early anaesthesiologists, obstetricians and – notably - dentists. Considered an *inert gas* for a long time, side effects were not a matter of interest. Today we know that – among other kinds of mischief - it:

- Is ineffective in comparison to volatile anaesthetics
- Is associated with high incidence of postoperative nausea and vomiting (PONV)
- Diffuses into air filled spaces
- Damages the heart and the brain
- Is toxic
- Kills patients
- Destroys the ozone layer

Today, there is no medical need for the use of N_2O as an anaesthetic

When N_2O started its career as an anaesthetic only few alternatives were available. Therefore, it was accepted that it was rather ineffective, as reflected by MAC_{50}-value of 107-114%. N_2O was used to supplement volatile agents such as Halothane, Enflurane and Isoflurane. It decreases the concentration of these inhalational anaesthetics, which have a much higher blood-gas coefficient than N_2O. Moreover, in earlier times, no opioids with short context-sensitive half-life were available. However, this has changed: Today there are well-tolerated short to ultra-short acting anaesthetic drugs available. Further, modern anaesthesia workstations allow low-flow anaesthesia with contemporary and inexpensive inhalational agents. Accordingly, there is no need for the use of N_2O. This is even more true, in consideration of it's side-effects, such as reducing myocardial contractility, increasing pulmonary-vascular and reno-vascular resistance, lowering glomerular filtration. Augmenting cerebral glucose metabolism and cerebral blood flow render it particularly unsuitable for neuroanaesthesia.

N_2O increases the incidence of PONV and postoperative infection

In the last 10 years two large studies were published on the influence of N_2O on morbidity and mortality, the so-called ENIGMA-I and ENIGMA-II trials (1, 2). ENIGMA-I randomized 2050 patients undergoing surgery for > 2h under general anaesthesia either with or without N_2O. The authors found in the N_2O group an increase in PONV, wound infection, pneumonia and fever.

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Moreover, patients in the control group were more likely to be discharged from the hospital on any given day. The observed increased infection rate might be caused by a leukocyte DNA Damage following N_2O administration (3). The ENIGMA-II trial randomized 7112 patients for major non-cardiac surgery under general anaesthesia, either with or without N_2O. That study confirmed that N_2O increases the risk of postoperative nausea and vomiting. Even in patients receiving PONV prophylaxis the incidence of PONV was increased when compared with patients receiving N_2O-free general anaesthesia without PONV prophylaxis (13.1 vs. 9.7%) (4).

N_2O causes harm by increasing the cuff pressure

N_2O diffuses into air-filled rooms in order to equalize the partial pressures of gases. Therefore, it increases the tube-cuff-pressure, enlarges pneumothorax and pneumencephalus, scales up the gas volume in the bowel, elevates middle-ear-pressure, and jeopardizes outcome of SF_6-based ophthalmic surgery. Although this is well known and N_2O is avoided in those clinical situations, it has to be realized that N_2O causes damage at the vocal cords or in the trachea due to the missing perception of a much too high cuff pressure (5, 6). Unfortunately, anaesthesiologists do not always check the cuff seal point after tracheal intubation and thereafter every 20-30 minutes, allowing for timely adjustment.

N_2O is toxic

How do we know? Most regulatory authorities have established a *Maximum Workplace Concentration* (100 ppm) and in most countries N_2O is listed in the *Hazardous Substances Ordinance*, which clearly indicates potential toxicity.

Most unacceptable for an "inert gas" is the effect on methionine synthetase, possibly resulting in anemia and leukopenia due to interference with megaloblastic myelopoesis. By oxidizing Cobalt, N_2O inactivates Vit B_{12} - a crucial coenzyme of methionine synthetase - and blocks synthesis of folic acid. Loss of methionine synthetase activity results in accumulation of *substrates* – e.g. homocysteine, 5-methyl-tetrahydrofolate - and diminution of *products* – e.g. methionine, tetrahydrofolate (7). Homocysteine, which is accumulated, is a risk factor for cardio- and cerebrovascular disease, thrombosis and stroke, neuronal damage and osteoporosis (8). Conversely, inhibition of methionine synthase induces depletion of intracellular tetrahydrofolate, which may compromise host defense mechanisms (3), which in turn may explain the increased infection rate seen in ENIGMA-I. Consequences of methionine- and tetrahydrofolate deficiency include not only an increase in infection rates, but also interference with myelin and – via thymidinsynthetase inhibition - DNA-synthesis and VitB_{12}-regeneration. The latter promotes bone marrow depression, resulting in megaloblastic anemia. Complications of Vit B_{12} deficiency – most prominent in elderly patients – appear two to eight weeks after exposure, hence way after the last post-anesthesia-visit. Such complications eventually may result in funicular myelosis, including ataxia and progressive paresis.

Concern that exposure to N_2O may cause mutagenic, carcinogenic, or teratogenic changes has prompted experimental and clinical studies. Fortunately, most tests for mutagenicity have given negative results. However, animal studies demonstrate that nitrous oxide can cause adverse reproductive effects. Fetal resorptions, congenital anomalies, and fetal growth retardation occur in rodents exposed to N_2O during a major portion of gestation. In addition, N_2O may alter male germ cells. Results of clinical studies are less clear; however, epidemiologic surveys of operating room and dental suite personnel indicate adverse reproductive effects (9, 10). One study demonstrated an increased incidence of spontaneous abortion among women exposed to waste anesthetic gases, specifically N_2O (11).

In addition to these pathophysiological problems N_2O is a gas which is toxic for the environment, since it destroys the ozone layer. N_2O is likely to be the most significant ozone depleting substance throughout the 21st century, and is the third most important greenhouse gas released into the atmosphere (12). Global anthropogenic N_2O, which originates by two-thirds from agriculture, is expected to almost double by 2050. Although medical N_2O is a minor contributor it is obvious that reducing the emission of medical N_2O is how we as anaesthesiologists can accept responsibility for the environment.

Fatal errors in N_2O delivery due to pipeline flaws

As if this wasn't enough N_2O holds a unique record of killing people by hypoxia, usually due to a fatal combination of technical error, lack of vigilance and poor judgement. In 2007 and Herff et al. (13) analysed N_20-associated fatalities in Germany, Austria and Switzerland receiving press coverage. They reported six fatalities from 2004 to 2006 caused by pipeline design flaws. Three of these had happened in 2004 in one community hospital in Saxony, where three consecutive parturients died from iatrogenic hypoxia during general anesthesia for C-section. In a follow-up-analysis of Internet-reports the same authors identified a total of 15 fatalities within six years (14). In all cases N_2O was administered instead of oxygen - although inspiratory oxygen monitoring is unequivocally mandated by the European technical standard EN 740 (Table 1).

The authors of this article urge to measure obligatorily and in all cases the inspiratory oxygen fraction and to use ORC (oxygen ratio control). Moreover, they advise that all anaesthesiologists involved should be informed about repair or construction of central gas supply tubes.

Conclusion

As anesthesiologists we are committed to *primum nihil nocere* more than any other medical specialty. Purposefully risking the well-being of our patients by increasing the risk of PONV, airway and vocal cords lesions and blocking our patient's methionine synthetase by a weak, dispensable anaesthetic clearly violates the tenet *Domitandes protegimus*. Accordingly N_2O is obsolete.

N2O? Just say NO!

Table 1. Fatalities from mistakes in nitrous oxide supply (modified from Herff et al. (14))

Case	Country	Surgery	Mistake	Reason	Source	Date
1.	Austria	Spine	Gas pipe in OR	New OR	Tiroler Tageszeitung	25.10.05
2.	Ger	Tibia fracture	Gas pipe in hospital	Repair	Süddeutsche Zeitung	26.03.06
3.	Ch	Cardiac	Gas pipe in OR	Unknown	Neue Züricher	04.04.04
4-6.	Ger	Sectio caes.	Gas pipe in anaesthesia maschine	Repair	ARD Tages-schau-Online	24.12.04
7.	GB	Trauma	Gas pipe in anaesthesia maschine	Unknown	BBC News Online	12.02.02
8+9.	USA	Routine anaesth	Gas pipe into hospital	Repair	New York Times	17.01.02
10-15.	Italy	ICU	Gas pipe in hospital	New ICU	La Republica	06.05.07

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